

Philip Livingston and Friedhelm Helling  
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claims 44-68 are pending upon entry of this Amendment.

Applicants hereinabove added claims 44-68. Support for new claims 44-54 can be found inter alia in the specification, specifically on page 11, line 13-page 12, line 2 and page 14-line 7-page 15, line 10. Support for new claims 55-68 can be found inter alia in the specification on page 15, line 12-page 18, line 9. Therefore, new claims 44-68 do not involve any issue of new matter. Accordingly, applicants respectfully requests that the Examiner enter new claims 44-68.

Applicants have further amended the specification to correct for minor, obvious clerical or typographical errors. Applicants have clarified the description of the figures to refer to specific figures. Applicants maintain that the amendments do not introduce new matter to the subject application. Accordingly, applicants respectfully request entry of these amendments.

The Examiner stated that the disclosure is objected to because of the following informalities.

The Examiner stated that on page 5, line 30, in Brief Description of the Figures, Figure 6b is listed as IgG antibodies but Figure 6b has the y-axis labeled as IgM titer. The Examiner stated that appropriate correction is required.

In response, applicants will submit a revised Figure 6B correctly labeling the y-axis as IgG when this case is in condition for allowance.

#### **Rejection Under 35 U.S.C. §101-Double Patenting**

The Examiner provisionally rejected claims 21-29 under 35 U.S.C. 101 as claiming the same invention as that of claims

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44-52 of copending application Serial No. 08/477,097 or 08/475,784. The Examiner stated that this is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The Examiner stated that claims 30-42 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 44-56 of copending application Serial No. 08/477,147 and 08/481,809. The Examiner stated that this is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The Examiner stated that claims 21-29 of this application conflict with claims 44-52 of application serial numbers 08/477,097 and 08/475,784.

Further, the Examiner stated that claims 30-42 of this application conflict with claims 44-56 of copending applications serial numbers 08/477,147 and 08/481,809.

The Examiner also stated that the claims 21-29, and 43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44-56 of copending application Serial Nos. 08/477,147 and 08/481,809. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because the method claims as recited in the copending applications encompass the composition as instantly claimed. The Examiner stated that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The Examiner stated that claims 30-42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

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claims 44-52 of copending application Serial Nos. 08/475,784 and 08/477,097. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because the method claims as recited in the copending application encompass the composition as instantly claimed.

In response to the provisional double patenting rejection, applicants point out that for a provisional double patenting rejection, M.P.E.P. §804 requires that the:

'provisional' double patenting rejection should continue to be made by the Examiner in each application as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in one of the applications. If the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the Examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the 'provisional' double patenting rejection in the application(s) into a double patenting rejection at the time the one application issues as a patent.

Therefore, applicants maintain that even if the Examiner continues to conclude that the claims of the subject application conflict with the claims of other U.S. applications, the provisional rejection should be withdrawn in view of applicants' arguments which overcome the other rejections of this application under sections 112 and 103. Thus, the subject application should be allowed to issue.

**Rejections Under 35 U.S.C. §112, second paragraph**

The Examiner rejected claims 21-43 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants

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regard as the invention.

The Examiner stated that claim 35 is rejected for being vague and indefinite for using the trademark "QS-21" since it is unclear what the metes and bounds of said trademark. The Examiner stated that since a product denoted by a trademark may at some time change it is suggested the trademark be accompanied with the generic terminology.

The Examiner stated that claim 35 is indefinite because it contains the abbreviation "QS-21". The Examiner stated that full terminology should be in each instance in the claims without the additional use of redundant abbreviations in parentheses or otherwise.

The Examiner stated that claims 21-43 are rejected since they refer to claims which have been canceled.

In response, applicants have hereinabove canceled claim 35 without prejudice and added new claim 61. New claim 61 also recites "QS-21." Applicants respectfully point out that QS-21 is not a trademark name of the aforementioned adjuvant. As discussed in Kensil, et al. (1991) J. Immunology 146: 433, QS-21 refers to an isolated sample of Quil-A, a commercial saponin derived from *Quillaja saponaria* Molina, commonly used in adjuvant studies, which was isolated by high-pressure liquid chromatography. Thus, the term "QS-21" is neither vague nor indefinite because the compound was well-known in the art prior to the filing of the application. Further the specification states on page 20, lines 13-14, that QS-21 is a saponin component of Quil-A. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the 35 U.S.C. §112 rejection.

Further, in response, applicants have hereinabove canceled claims 21-43 without prejudice and added new claims 44-68 which

correspond to canceled claims 21-43 but are not dependent on canceled claims. Accordingly, new claims 44-68 render the Examiner's rejection moot.

**Rejection Under 35 U.S.C. §112, first paragraph**

The Examiner rejected claims 21-43 and objected to the specification under 35 U.S.C. § 112, first paragraph as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The Examiner stated that the specification teaches a method for preparing GD3 and GM2 ganglioside conjugate vaccines. The Examiner stated that the specification also teaches that immunization of mice with the GD3-Keyhole Limpet Hemocyanin (GD3-KLH) conjugate generated the highest titer of IgM and IgG responses compared to the other conjugates tested and that the sera was highly specific for GD3 in human tissue extracts. The Examiner stated that the specification teaches that melanoma patients immunized with the GM2-KLH generated high titers of IgM and IgG antibodies. The Examiner stated that the specification does not teach that the production of antibodies to GD3-KLH or GM2-KLH results in the treatment of the cancer. The Examiner stated that the production of antibodies upon administration of a ganglioside conjugate vaccine cannot be extrapolated to the ability of the antibodies to prevent or treat cancer since in a previous study (see Fung et al.), no significant prolongation of survival was observed in mice that were administered a GM2-KLH conjugate vaccine, despite the ability of GM2-KLH to produce of high titers of anti-GM2 IgG antibodies. The Examiner stated that therefore, the production of antibodies upon administration of a ganglioside conjugate vaccine is not sufficient to insure that these antibodies will prevent cancer.

In response, applicants respectfully traverse the above ground of rejection. Applicants maintain that the claimed invention has

been fully enabled by the disclosure in the application.

Specifically, applicants would like to point out that Fung et al. should not be used to assess either the immunogenicity or efficacy of ganglioside conjugate vaccines. Fung et al. studied active specific immunotherapy of a murine mammary adenocarcinoma using a vaccine composed of the Thomsen Freidenreich hapten coupled to KLH and emulsified in Ribi adjuvant. See Fung et al., Abstract, lines 3-5. A GM2-KLH conjugate vaccine served only as an experimental control using an unrelated hapten in order to exclude nonspecific effects. See Fung et al., Page 4310. There is no evidence presented in Fung et al. to show that the studied cancer cells express GM2, nor is there evidence to show that GM2 antibodies were generated after vaccination. It is clear that the Fung et al. experiments were not designed to evaluate either the immunogenicity or efficacy of a ganglioside conjugate vaccine.

The Examiner stated that the specification also does not provide guidance on the synthesis of conjugates with other gangliosides or chemically modified gangliosides. The Examiner stated that as described in the specification the ganglioside region of attachment to the carrier protein is important in maintaining the antigenicity of the ganglioside. The Examiner stated that due to the variations in both the carbohydrate and ceramide portions of various gangliosides, it is not clear if the method used to conjugate GD3 and GM2 to KLH could be applied to other gangliosides and still maintain the antigenicity of other gangliosides. The Examiner stated that the specification also does not provide guidance on the synthesis of derivatives of KLH not does the specification teach which derivatives would result in an enhanced antibody response.

In response, applicants traverse the above ground of rejection. Applicants maintain that enough guidance has been provided by the

applicants' disclosure on the synthesis of conjugates with other gangliosides or chemically modified gangliosides. Namely, the "[g]anglioside conjugation must be accomplished without altering the immune dominant carbohydrate moiety." See Specification, page 32, lines 6-13. Applicants have also provide specific procedures by which one skilled in the art could produce a conjugate comprising an immunogenic protein and a ganglioside that retains its antigenicity. See e.g. Specification, Page 21, line 29-page 23, line 19; page 24, line 15-page 26, line 25, line 32; page 43, line 26-page 50, line 11.

Regarding the Examiner's comments about the derivatives of KLH, applicants maintain the specification provides enabling teachings to generate such derivatives. Fragments of KLH may be generated by routine experiments such as limited proteolysis. Different modified forms of KLH may also be produced by routine experimentation. These derivatives may then be tested with their immunogenicity using the procedures disclosed in the specification. Only derivatives which are immunogenic will be selected. Accordingly, applicants maintain that the specification provides enough guidance to synthesize derivatives of KLH which would be effective in the subject vaccine.

In view of the foregoing, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

#### **Rejection Under 35 U.S.C. §103**

The Examiner rejected claims 21, 26-34, 36, and 39-43 under 35 U.S.C. § 103 as being unpatentable over Livingston et al. (Cancer Research) in view of Ritter et al. (1991) and Livingston et al. (U.S. Pat. No. 5,102,663) and Ritter et al. (1990).

The Examiner stated that Livingston et al. (Cancer Research)

teach a vaccine administered to melanoma patients for stimulating the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2. The Examiner stated that Livingston et al teach that the vaccine is administered at a concentrations of 100, 200, or 300 ug with an adjuvant, Bacillus Calmette-Guerin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline. The Examiner stated that Livingston et al teach that melanoma recurrence was delayed in patients developing GM2 antibodies after vaccination. The Examiner stated that Livingston et al. teach that more patients produced IgM antibodies than IgG antibodies to the GM2. The Examiner stated that Livingston et al. also teach the gangliosides GM2, GD2, and GD3 are expressed on the cell surface of human malignant melanomas.

The Examiner conceded that Livingston et al. (Cancer Research) do not teach the conjugation of the GM2 vaccine with Keyhole Limpet Hemocyanin (KLH). The Examiner also conceded that Livingston et al. do not teach the use of any other gangliosides in a vaccine preparation.

The Examiner stated that Ritter et al (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response. The Examiner stated that Ritter et al discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG a) has a higher affinity; b) is better able to penetrate solid tissues; c) is able to mediate antibody-dependent cell-mediated cytotoxicity; d) and is generally detectable in the serum for longer periods after immunization. The Examiner stated that Livingston et al. (U.S. Pat. No. 5,102,663) teach that the gangliosides GM3, GM2, GD3, GD2, GT3, and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of



neuroectodermal origin. The Examiner stated that Ritter et al (1990) teach that GD3 derivatives such as GD3 lactone are more immunogenic than GD3.

The Examiner asserted that it would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al. by conjugating the GM2 ganglioside to KLH, or to a derivative of KLH, because the conjugated vaccine would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages taught above by Ritter et al (1991). The Examiner further asserted that it would have also have been obvious to substitute any of the gangliosides GM3, GD2, GD3, GT3 or O-acetyl GD3 for the GM2 ganglioside in the vaccine because they are all prominent cell-membrane components of melanoma as taught by Livingston et al. and one of ordinary skill in the art would expect that IgG antibodies against these gangliosides would react with the melanoma cells. The Examiner asserted that it would also have been obvious to substitute GD3 lactone for the GM2 ganglioside in the vaccine because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al (1990), and would be expected to produce and enhanced antibody response compared to GD3.

The Examiner stated that optimization of the dosage, route of administration, and number of sites to administer the composition is within the skill of the ordinary artisan.

In response, applicants respectfully traverse the Examiner's §103 rejection. Applicants have hereinabove cancelled claims 21, 26-34, 36, and 39-43 without prejudice. New claims 44-60, 62 and 65-68 corresponds to the cancelled claims 26-34, 36, and 39-43 which are directed to ganglioside conjugate vaccine comprising a ganglioside conjugated to an immunogenic protein effective to stimulate or enhance antibody production in a subject, an effective amount of adjuvant and a pharmaceutically acceptable

vehicle and methods of using such vaccines.

Livingston et al. discuss immunizing melanoma patients with a vaccine composed of a ganglioside, GM2, mixed with adjuvant BCG. Conceded by the Examiner, Livingston, et al. do not disclose or teach a ganglioside conjugate vaccine, and therefore this article does not disclose or teach the claimed invention.

The applicants' claimed vaccine which comprises (1) a ganglioside conjugate which maintains the antigenicity of the oligosaccharide portion of the ganglioside, (2) an effective amount of adjuvant and (3) a pharmaceutically acceptable carrier. Ritter et al. (1991) do not disclose or teach a ganglioside conjugate wherein the antigenicity of the oligosaccharide portion of the ganglioside remains intact. Ritter et al. (1991) do not disclose or teach the use of adjuvants. As previously stated, applicants' specification clearly teaches the importance of maintaining the antigenicity of the oligosaccharide portion of the ganglioside and incorporating of an adjuvant in the claimed vaccine. Accordingly, Ritter et al. (1991) do not disclose or teach the claimed invention.

Livingston et al. (U.S. Patent 5,102,663) discuss a specific vaccine composed of only the 9-O-acetyl GD3 ganglioside and an adjuvant. Livingston et al. never disclose nor teach conjugation of a ganglioside with any immunogenic protein.

Ritter et al. (1990) disclose GD3 derivatives, specifically GD3 lactone, induced antibody responses in mice. Ritter et al. do not suggest or motivate one skilled in the art to practice a ganglioside conjugate vaccine.

Even in combination, the cited references do not suggest or motivate a person of ordinary skill in the art to practice the subject invention. Regarding the Examiner's statement that "it

would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al. by conjugating the GM2 ganglioside to KLH, or to a derivative of KLH, because the conjugated vaccine would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991)," applicants would like to point out that even assuming, arguendo, that an ordinary skilled artisan may be motivated to try to make a useful ganglioside vaccine, there is no reasonable expectation of success for such attempt because as discussed hereinabove the antigenicity of the oligosaccharide portion of the ganglioside needs to be maintained during conjugation and an adjuvant needs to be included in the claimed vaccine. This guidance is only provided by the applicants' specification. Accordingly, applicants maintain that the combination of the cited references does not render the claimed invention obvious and respectfully request that the Examiner reconsider and withdraw the above ground of rejection.

The Examiner rejected claim 35 as being unpatentable over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et al (U.S. pat 5,102,663) and Ritter et al (1990) in view of Kensil et al and Marciani et al.

The Examiner stated that the teachings of Livingston et al and Ritter et al and Livingston et al and Ritter et al are set forth above. The Examiner acknowledged that the above cited art does not teach the use of QS-21 as an adjuvant.

The Examiner stated that Kensil et al teach that QS-21 produced a higher antibody response than aluminum hydroxide. The Examiner stated that Kensil et al also teach that the immune responses obtained with QS-21 reached a plateau at doses between 10 and 80 ug in mice. The Examiner stated that Marciani et al teach the use of QS-21 as an adjuvant in a vaccine at concentrations of 10 and 20  $\mu$ g. The Examiner stated that Marciani et al also teach

that the QS-21 adjuvant did not cause a toxic reaction in cats. The Examiner asserted that it would have been obvious to one of ordinary skill in the art to add QS-21 as an adjuvant to the vaccine taught by the above cited art because QS-21 produces a higher antibody response than the commonly used adjuvant, aluminum hydroxide, as taught by Kensil et al, and QS-21 is not toxic to animals as taught by Marciani et al. Further, the Examiner asserted that it would also have been obvious to use doses of between 10 and 200 ug because the immune response obtained with QS-21 plateaus at doses between 10 and 80 ug and optimization of the dose according to the subject receiving the vaccine is within the skill of the ordinary artisan.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants have cancelled claim 35 hereinabove without prejudice. Claim 61 corresponds to the cancelled claim 35 which is directed to a method comprising administration of an effective amount of vaccine composed of a ganglioside conjugated to an immunogenic protein effective to stimulate or enhance antibody production in the subject, an effective amount of QS-21, and a pharmaceutically acceptable vehicle.

Applicants have already discussed Livingston et al. (Cancer Res) and Ritter et al. (1991) and Livingston et al. (U.S. Patent 5,102.663) and Ritter et al. (1990) hereinabove and would like to reiterate their prior position here. Kensil et al. and Marciani et al. teach uses of QS21 as an adjuvant but they do not disclose ganglioside conjugate vaccines. As applicants have discussed hereinabove, none of the other references cited by the Examiner discloses, suggests or motivates an ordinary skilled artisan to make applicants' claimed invention. Even in combination, the cited references do not suggest or motivate a person of ordinary skill in the art to practice the subject invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the above §103 rejection.

The Examiner rejected claims 22-25, 37 and 38 under 35 U.S.C. § 103 as being unpatentable over Livingston et al (Cancer Res) in view of Ritter et al (1991) and Livingston et al (U.S. Pat 5,102,663) and Ritter et al (1990) as applied to claims 21, 26-34, 36, and 39-43 above, and further in view of Irie et al.

The Examiner stated that the teachings of Livingston et al (Cancer Res) and Ritter et al (1991) and Livingston et al (U.S. pat 5,102,663) and Ritter et al (1990) are set forth above. It would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston et al by conjugating the GM2, or other gangliosides, to KLH for the reasons set forth above. The above cited art does not teach administration of the vaccine for treating cancer of epithelial origin or for producing antibodies to gangliosides found in the stroma of cancer.

The Examiner stated that Irie et al teach that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas. The Examiner asserted that it would have been obvious to one of ordinary skill in the art to administer the vaccine taught by the above cited art to patients afflicted with or susceptible to cancer of an epithelial origin (e.g. breast carcinomas) because the ganglioside GM2 is found in the stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the vaccine react with the tumor and either treat or prevent the cancer.

In response, applicants respectfully traverse the above rejection. Applicants have cancelled claims 22-25, 37 and 38 without prejudice. Claims 47-50, 63 and 64 corresponds to claims 22-25, 37 and 38. These claims are directed to ganglioside conjugate vaccine and methods using same which will be used against cancer wherein the gangliosides are found either in stroma or epithelium.

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Applicants have discussed Livingston et al. (Cancer Res) and Ritter et al. (1991) and Livingston et al. (U.S. Patent 5,102,663) and Ritter et al. (1990) hereinabove and would like to reiterate their prior position here. The fact that Irie et al. teach that GM2 is found in several cancer types does not disclose or teach the applicants' claimed invention. As applicants have discussed hereinabove, none of the other references cited by the Examiner discloses, suggests or motivates an ordinary skilled artisan to make applicants' claimed invention. Even in combination, the cited references do not suggest or motivate a person of ordinary skill in the art to practice the subject invention. Accordingly, in view of the foregoing, applicants respectfully request that the Examiner reconsider and withdraw the above §103 rejection.

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the June 13, 1996 Office Action and earnestly solicit allowance of the claims now pending in the subject application, namely claims 44-68.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the \$465.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any other fee is required,

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authorization is hereby given to charge the amount of any such  
fee to Deposit Account No. 03-3125.

Respectfully submitted,

Albert Wai Kit Chan

I hereby certify that this correspondence  
is being deposited this date with the  
U.S. Postal Service with sufficient  
postage as first class mail in an  
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